

COMMENTARY

Mechanistic Vs. Empirical Network Models of Drug Action

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Declining success rates coupled with increased costs is leading to an inevitable breaking point in the drug development pipeline. Can we avoid it by incorporating the vast mechanistic understanding of drug action? A recent review highlights this dilemma and proposes “quantitative logic gate” modeling as a solution.¹ The goal of this commentary is to contrast this approach with mechanistic biochemical network models, which, although alluded to by Kirouac and Onsum, requires a closer analysis.

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Although the drug development pipeline may be construed differently, many believe that it is important to have a computational modeling layer to explore, in a relatively inexpensive manner, potential scenarios for how drugs may be used. This computational layer has been embodied in model-based drug development (MBDD)—supported by regulatory agencies and industry alike—yet newer systems-based approaches will likely impact the future of MBDD. It is posited that systems-based modeling, due to its ability to predict drug effects on cell-signaling networks, will have a large impact and lend confidence to MBDD. Even though many types of systems-based approaches exist, they share a pervasive feature of being quantitative.²

In their recent review, Kirouac and Onsum promote one particular approach to systems-based signal transduction modeling in the context of MBDD for oncology termed “quantitative logic” (QL).¹ QL models incorporate some notion of connectivity between central nodes of cell-signaling networks, yet retain the ease-of-implementation of coarse-grained, empirical representations. At the core, QL is the widely used Hill-type equation, which generally relates the magnitude of an input X to the magnitude of an output Y via a sigmoidal relationship (Figure 1a). QL, via alterations to the Hill equation, can account for multiple inputs having additive, synergistic or antagonistic effects on the output by accounting for various wirings, such as “OR,” where two inputs have independent but additive effects on Y (Figure 1b), or “AND,” where two inputs are simultaneously needed to increase Y (Figure 1c). The authors similarly suggest how, using principles of linear dynamical systems theory, one may incorporate time-dependency into QL that necessarily increases the number of empirical parameters and the amount of data needed to constrain the model.

Four hallmarks of cell-signaling networks—modularity, redundancy, adaptation, and heterogeneity—are offered as support for QL approaches in drug development; in essence, arguing that condensed, nonspecific networks of QL models will capture signaling dynamics although remaining relatively easy to develop.³ This feature is attained by coarse-graining the underlying complexity of the signal transduction network. Importantly, however, this empirical coarse-graining comes with trade-offs that may limit the applicability of QL to MBDD

because (i) apart from new, explicitly designed experiments, there is no clear way to predict how new drugs or drug combinations affect signaling network behavior; (ii) interpreting the quantitative effects of common genetic variations or mutations is not straightforward; (iii) capturing cell-to-cell heterogeneity requires empirical sampling approaches whose consistency with known biological variation is not well understood; and (iv) scaling preclinical model parameters to patient models without a biochemical foundation will be difficult.⁴ Mechanistic, or physiochemical models of signal transduction networks, however, are based on fundamental biophysical assumptions and provide a direct means to addressing these four issues (illustrated below), albeit at the cost of having more complex, larger models. By no means are mechanistic models (MMs) a panacea, yet the network specificity MMs represent seems to offer potential solutions to these shortcomings of QL models.

As a test case, we consider a previously published MM of receptor tyrosine kinase signaling⁵ that relates epidermal growth factor— and heregulin- β —induced activation of the ErbB (aka HER) receptors to activation of ERK and Akt (Figure 2a), two central pathway end points controlling proliferation and apoptosis. Underlying this simplified schematic is a system of 117 ordinary differential equations that were mainly derived based on chemical kinetics theory. Similar to Figure 4 of the Kirouac and Onsum review,¹ it can also be cast as a QL model (Figure 2b), where for simplicity of this commentary we consider only ErbB1 (aka EGFR) and ErbB3 receptors. We used the MM to simulate how active ERK and active Akt levels (denoted by *) depend on levels of active ErbB1 (pErbB1) and active ErbB3 (pErbB3) 30 min after epidermal growth factor or heregulin- β stimulus (approaching a steady-state), and then considered these as data with which to build the QL model (see **Supplementary Data** online for MATLAB files; The Mathworks, Natick, MA). Figure 2c shows that the QL model (solid lines) provides an excellent description of the simulated data (X symbols) for how both active ERK and Akt levels depend on active receptor levels. Therefore, both model types provide quantitative descriptions of this cell-signaling network, as expected.

An important goal of MBDD is to predict the effects of new drugs or new drug combinations before extensive experimental testing (point (i) above). We consider predicting whether

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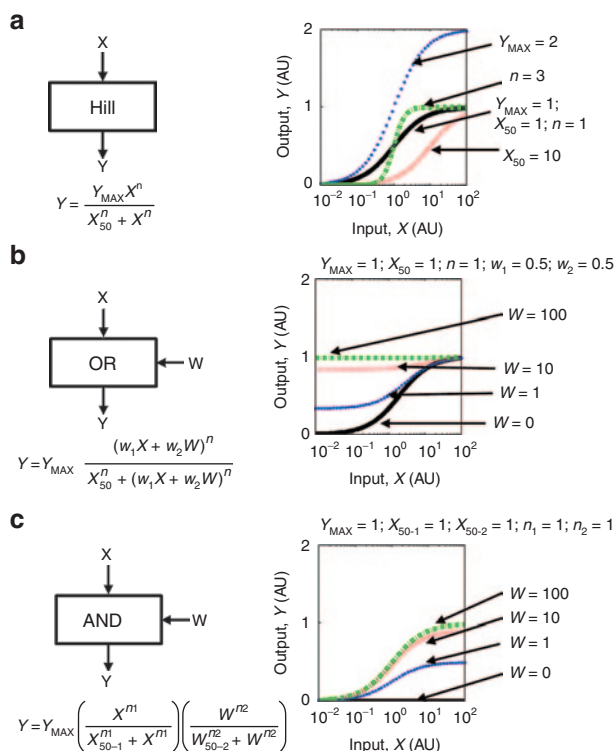


Figure 1 Overview of QL functions and behavior. **(a)** A basic Hill function relating the input X to the output Y . Y_{MAX} is the maximum possible value Y can admit, X_{50} is the input magnitude causing half-maximal output (i.e., $Y = Y_{\text{MAX}}/2$), and n is the Hill coefficient that determines the “steepness” of the response. The X – Y relationships are plotted for various parameter values (equal to 1 unless indicated otherwise). **(b)** The QL OR function which combines inputs X and W to yield the output Y . The effect of increasing the 2nd input W is shown in the plot, for parameter values as indicated at the top of the plot. **(c)** The QL AND function which also combines inputs X and W to yield the output Y . The effect of increasing the 2nd input W is shown in the plot, for parameter values as indicated at the top of the plot. QL, quantitative logic.

combining a low affinity, competitive Raf inhibitor having a 100 nmol/l inhibition constant with a competitive ErbB1 inhibitor with 10 nmol/l affinity for ErbB1 and ErbB2 (e.g., lapatinib) would be an effective way to block 10 nmol/l epidermal growth factor–driven ERK signaling, given 100 nmol/l drug concentrations. In the MM, by simply altering the rate equation for Raf-catalyzed phosphorylation of MEK in a manner consistent with competitive inhibition, and likewise for the receptor inhibitor, the MM predicts a modest 58% decrease in ERK* (**Figure 2d**). To recapitulate these effects with a QL model, we try decreasing the level of pErbB1 by 90% (strong receptor inhibitor) and increasing the X_{50} of the ERK* OR function by 25% (weak Raf inhibitor). Under these conditions, the QL model predicts a 77% decrease in ERK* (**Figure 2d**).

The QL model predictions differ substantially from those of the MM, to the point where it may alter decision making. Why? One likely major reason is that in defining modularity based on Figure 4 of ref. 1, the QL model is missing the key dynamics that are necessary to predicting drug response. Therefore, using additional experimental data and creating cascades of QL-submodel networks, such as considering PI-3K, Raf, and

MEK independently, should yield improved predictions. However, it remains unclear on how to define such finer-grained modules *a priori* and also how to implement the mechanistic effects of new drugs precisely. What parameters of the QL model do we alter to make new drug predictions such as those considered above, and by how much do we alter them? Therefore, we would argue that MM predictions, which allow for a direct interpretation and implementation of drug action, have more value in MBDD.

Another goal of MBDD is personalized medicine: making predictions based on parameters that are specific to particular patients. In the context of oncology, this predominantly means incorporating the effects of genetic mutations into predictions (point (ii) above).⁶ One very common genetic aberration is an activating PI-3K mutation; we consider one that raises its catalytic activity by threefold. In the MM, simulating the effects of this mutation on ERK* and Akt* levels is straightforward; simply increasing the k_{cat} for PI-3K by threefold causes a tenfold increase in Akt* and a 1.43-fold increase in ERK* (**Figure 2e**). For the QL model, again however, without explicit experimental data, it is not clear on how we might alter the parameters to implement the PI-3K mutation. We attempt to simulate this mutation by decreasing the X_{50} values for the Akt OR function by 100%, which predicts a 1.6-fold increase in Akt* and no change in ERK*. These QL simulation results are again quite different from those of the MM; the above discussion applies here also.

It is becoming increasingly appreciated that cellular heterogeneity plays a major role in anticancer drug sensitivity and resistance (point (iii) above), and one mechanism by which this occurs is gene expression noise: natural variation in protein levels from cell to cell. Several studies have shown that such variations can be accounted for in MMs by sampling initial protein level conditions from biologically reasonable distributions, and subsequently looking at the distribution of signaling outputs.^{7,8} How can one perform such simulations in a QL framework? As suggested by Kiruoac and Onsum,¹ one can sample the various parameters of the QL model and perform several simulations, but which ones do we sample, from what distribution, and what is their variance? These questions are difficult if not impossible to answer due to the empirical nature of QL models.

The aforementioned examples simply illustrate the fact that as QL models are empirical, they have difficulties making predictions outside the experimental data for which they were trained. MMs, however, allow for such extrapolative predictions because their parameters and variables have explicit physical meaning. However, there are currently many issues with MMs that must be solved before they are practically useful. Model identifiability is a major one; it is not currently understood on how to design experiments such that we have high confidence in both the model structure and its estimated parameter values. This problem is diminished by “sloppiness,”⁹ where parameter uncertainty has small effects on predictions; however, it is unclear *a priori* to which predictions sloppiness applies. Moreover, in some situations, our mechanistic knowledge is incomplete, necessitating the use of empirical methods, for which such QL approaches may be appropriate. In the absence of biochemical data, QL methods might serve to codify qualitative relationships and guide

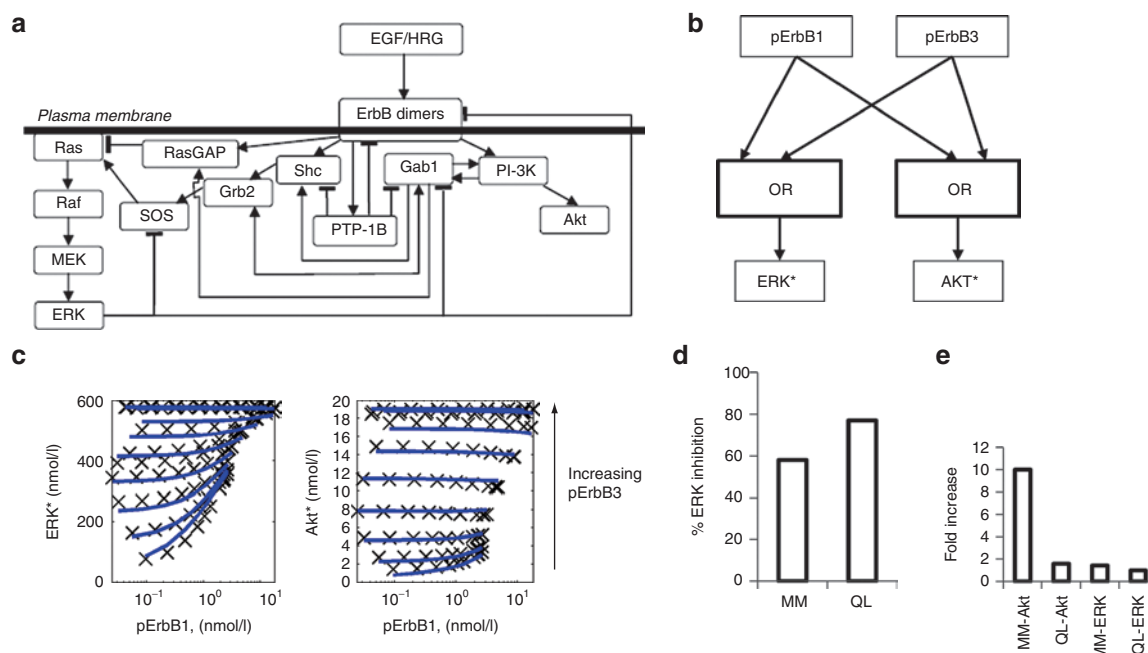


Figure 2 Comparing a MM with a QL model. **(a)** A simplified schematic of an MM for ErbB receptor signaling, adapted with permission from Birtwistle *et al.*, 2007. **(b)** A QL representation of ErbB signaling along the lines of Figure 4, Kiruoac and Onsum.¹ **(c)** Simulated ERK and Akt activation 30 min after EGF and/or HRG stimulus (various doses and combinations) as a function of active ErbB1 and ErbB3 levels. Black X symbols correspond to MM simulations and solid blue lines correspond to QL fit of model simulations. QL model parameters were estimated by fitting to the MM simulation data using the MATLAB function lsqnonlin (see **Supplementary Data** online) and $Y_{MAX} = 593.5$; $X_{50} = 1.34$; $n = 0.92$; $w_1 = 0.79$; $w_2 = 0.99$ for the ERK OR function and $Y_{MAX} = 19.6$; $X_{50} = 2.26$; $n = 1.08$; $w_1 = 0.15$; $w_2 = 0.89$ for the Akt OR function. The various curves on each plot depict different levels of pErbB3, with increasing amounts of pErbB3 shifting the curves upward. **(d)** Predicted % inhibition of active ERK 30 min after 10 nmol/l EGF stimulation in the presence of a strong receptor inhibitor and weak Raf inhibitor as described in the main text. **(e)** Predicted fold-increase in Akt and ERK signaling 30 min after 10 nmol/l EGF stimulus as a consequence of a PI-3K mutation. Increases in Akt signaling are the first two columns, and ERK are the last two columns. EGF, epidermal growth factor; HRG, heregulin- β ; MM, mechanistic model; QL, quantitative logic.


the experimentation and mathematical modeling required to develop MMs. In fact, combining QL and MM approaches into a hybrid model is a viable option that retains a mechanistic grounding and relaxes identifiability issues. Recent theoretical approaches to guaranteeing observability of large-scale nonlinear systems¹⁰ may be useful in such efforts. Nevertheless, based on the arguments presented above, we conclude that in the long term, MMs are better suited for the ultimate purposes of MBDD and tailored chemotherapy.

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